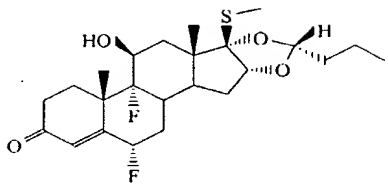

R1 cont.

fluticasone, fluticasone propionate and budesonide. These agents can be formulated for inhalation therapy.

Please replace the paragraph on page 9, lines 21-29, with the following paragraph:

As used herein, a nebulizer is an instrument that is capable of generating very fine liquid droplets for inhalation into the lung. Within this instrument, the nebulizing liquid or solution is atomized into a mist of droplets with a broad size distribution by methods known to those of skill in the art, including, but not limited to, compressed air, ultrasonic waves, or a vibrating orifice. Nebulizers may futher contain, *e.g.*, a baffle which, along with the housing of the instrument, selectively removes large droplets from the mist by impaction. Thus, the mist inhaled into the lung contains fine aerosol droplets.

R2

Please replace the paragraph beginning on page 10, line 19, through the paragraph on page 11, line 24, with the following paragraph:

As used herein, pharmaceutically acceptable derivatives of a compound include salts, esters, enol ethers, enol esters, acids, bases, solvates, hydrates or prodrugs thereof. Such derivatives may be readily prepared by those of skill in this art using known methods for such derivatization. The compounds produced may be administered to animals or humans without substantial toxic effects and either are pharmaceutically active or are prodrugs. Pharmaceutically acceptable salts include, but are not limited to, amine salts, such as but not limited to N,N'-dibenzylethylenediamine, chloroprocaine, choline, ammonia, diethanolamine and other hydroxyalkylamines, ethylenediamine, N-methylglucamine, procaine, N-

R3

benzylphenethylamine, 1-para-chlorobenzyl-2-pyrrolidin-1'-ylmethyl-benzimidazole, diethylamine and other alkylamines, piperazine and tris(hydroxy-methyl)aminomethane; alkali metal salts, such as but not limited to lithium, potassium and sodium; alkali earth metal salts, such as but not limited to barium, calcium and magnesium; transition metal salts, such as but not limited to zinc; and other metal salts, such as but not limited to sodium hydrogen phosphate and disodium phosphate; and also including, but not limited to, salts of mineral acids, such as but not limited to hydrochlorides and sulfates; and salts of organic acids, such as but not limited to acetates, lactates, malates, tartrates, citrates, ascorbates, succinates, butyrates, valerates and fumarates. Pharmaceutically acceptable esters include, but are not limited to, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl esters of acidic groups, including, but not limited to, carboxylic acids, phosphoric acids, phosphinic acids, sulfonic acids, sulfinic acids and boronic acids. Pharmaceutically acceptable enol ethers include, but are not limited to, derivatives of formula C=C(OR) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl. Pharmaceutically acceptable enol esters include, but are not limited to, derivatives of formula C=C(OC(O)R) where R is hydrogen, alkyl, alkenyl, alkynyl, aryl, heteroaryl, aralkyl, heteroaralkyl, cycloalkyl and heterocyclyl. Pharmaceutically acceptable solvates and hydrates are complexes of a compound with one or more solvent or water molecule, preferably 1 to about 100, more preferably 1 to about 10, most preferably one to about 2, 3 or 4, solvent or water molecules. Formoterol salts and hydrates are used in certain embodiments herein.

R3 cont.

Please replace the paragraph on page 16, lines 11-19, with the following paragraph:

R4

In one embodiment, the β_2-adrenoreceptor agonist is formoterol, or a pharmaceutically acceptable derivative thereof. In other embodiments, the

formoterol for use in the compositions provided herein is formoterol fumarate. Formoterol refers to 2-hydroxy-5-((1RS)-1-hydroxy-2-(((1RS)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide; or a stereoisomer thereof. The term formoterol also refers herein to the single enantiomers 2-hydroxy-5-((1S)-1-hydroxy-2-(((1S)-2-(p-methoxyphenyl)-1-methylethyl)amino)ethyl)formanilide and 2-hydroxy-5-((1R)-1-hydroxy-2-(((1R)-2-(p-methoxyphenyl)-1-methylethyl)-amino)ethyl)formanilide.

Please replace the paragraph on page 17, lines 9-17, with the following paragraph:

The compositions provided herein further contain, in addition to a β_2-adrenoreceptor agonist, including formoterol, a steroidal anti-inflammatory agent, including, but not limited to, budesonide or fluticasone propionate. Budesonide is (RS)-11β,16α,17,21-tetrahydroxypregna-1,4-diene-3,20-dione cyclic 16,17-acetal with butraldehyde. Budesonide also refers to the (R) isomer, the (S) isomer, and mixtures thereof. Fluticasone propionate refers to (6α,11β,16α,17α)-6,9-difluoro-11-hydroxy-16-methyl-3-oxo-17-(1-oxopropoxy)androsta-1,4-diene-17-carbothioic acid, S-fluoromethyl ester.

Please replace the paragraph beginning on page 19, line 5, through the paragraph on page 20, line 17, with the following paragraph:

In other of the above embodiments, the compositions further contain a buffer, including, but not limited to, citric acid/phosphate, acetate, barbital, borate, Britton-Robinson, cacodylate, citrate, collidine, formate, maleate, McIlvaine, phosphate, Prideaux-Ward, succinate, citrate-phosphate-borate (Teorell-Stanhagen), veronal acetate, MES (2-(N-morpholino)ethanesulfonic acid), BIS-TRIS (bis(2-hydroxyethyl)iminotris(hydroxymethyl)methane), ADA (N-(2-acetamido)-2-iminodiacetic acid), ACES (N-(carbamoylmethyl)-2-aminoethanesulfonaic acid), PIPES (piperazine-N,N'-bis(2-ethanesulfonic acid)), MOPSO (3-(N-morpholino)-2-hydroxypropanesulfonic acid), BIS-TRIS PROPANE (1,3-bis(tris(hydroxymethyl)methylamino)propane), BES (N,N-bis(2-

hydroxyethyl)-2-aminoethanesulfonaic acid), MOPS (3-(N-morpholino)propanesulfonic acid), TES (N-tris(hydroxymethyl)methyl-2-aminoethanesulfonic acid), HEPES (N-(2-hydroxyethyl)piperazine-N'-(2-ethanesulfonic acid), DIPSO (3-(N,N-bis(2-hydroxyethyl)amino)-2-hydroxypropanesulfonic acid), MOBS (4-(N-morpholino)butanesulfonic acid), TAPSO (3-(N-tris(hydroxymethyl)methylamino)-2-hydroxypropanesulfonic acid), TRIZMA® (tris(hydroxymethylaminomethane), HEPPSO (N-(2-hydroxyethyl)piperazine-N'-(2-hydroxypropanesulfonic acid), POPSO (piperazine-N,N'-bis(2-hydroxypropanesulfonic acid)), TEA (triethanolamine), EPPS (N-(2-hydroxyethyl)piperazine-N'-(3-propanesulfonic acid), TRICINE (N-tris(hydroxy-methyl)methylglycine), GLY-GLY (glycylglycine), BICINE (N,N-bis(2-hydroxyethyl)glycine), HEPBS (N-(2-hydroxyethyl)piperazine-N'-(4-butanesulfonic acid)), TAPS (N-tris(hydroxymethyl)methyl-3-aminopropanesulfonic acid), AMPD (2-amino-2-methyl-1,3-propanediol), and/or any other buffers known to those of skill in the art. In one embodiment, the buffer is citric acid/phosphate buffer, acetate buffer, citrate buffer or phosphate buffer. In another embodiment, the buffer is a citrate buffer (citric acid/sodium citrate). The buffer concentration has been found herein to affect the stability of the composition. Buffer concentrations for use herein include from about 0 or 0.01 mM to about 150 mM, or about 1 mM to about 20 mM. In one embodiment, the buffer concentration is about 5 mM. In another embodiment, the buffer concentration is about 1 mM to about 50 mM, or about 20 mM. The kinetic-pH profile of formoterol is dependent on buffer concentration. At low and approximately neutral conditions, increasing the buffer concentration from 5 mM to 20 mM increased the rate constant of decomposition significantly. However, no noticeable differences in rate constant were observed in the pH region of about 4.5 to about 5.5 with increasing buffer concentration from 5 mM to 20 mM. The particular buffer and buffer concentration of a given composition for long

B6 CONT. term storage provided herein may be determined empirically using standard stability assays well known to those of skill in the art (see, *e.g.*, the Examples).

Please replace the paragraph beginning on page 20, line 29, through the paragraph on page 21, line 28, with the following paragraph:

In embodiments where the pharamacologically suitable fluid is a saline solution, tonicity adjusting agents may be added to provide the desired ionic strength. Tonicity adjusting agents for use herein include those which display no or only negligible pharmacological activity after administration. Both inorganic and organic tonicity adjusting agents may be used in the compositions provided herein. Tonicity adjusting agents include, but are not limited to, ammonium carbonate, ammonium chloride, ammonium lactate, ammonium nitrate, ammonium phosphate, ammonium sulfate, ascorbic acid, bismuth sodium tartrate, boric acid, calcium chloride, calcium disodium edetate, calcium gluconate, calcium lactate, citric acid, dextrose, diethanolamine, dimethylsulfoxide, edetate disodium, edetate trisodium monohydrate, fluorescein sodium, fructose, galactose, glycerin, lactic acid, lactose, magnesium chloride, magnesium sulfate, mannitol, polyethylene glycol, potassium acetate, potassium chlorate, potassium chloride, potassium iodide, potassium nitrate, potassium phosphate, potassium sulfate, propylene glycol, silver nitrate, sodium acetate, sodium bicarbonate, sodium biphosphate, sodium bisulfite, sodium borate, sodium bromide, sodium cacodylate, sodium carbonate, sodium chloride, sodium citrate, sodium iodide, sodium lactate, sodium metabisulfite, sodium nitrate, sodium nitrite, sodium phosphate, sodium propionate, sodium succinate, sodium sulfate, sodium sulfite, sodium tartrate, sodium thiosulfate, sorbitol, sucrose, tartaric acid, triethanolamine, urea, urethan, uridine and zinc sulfate. In certain embodiments, the tonicity adjusting agent is sodium chloride, which is present at a concentration of from about 0 mg/mL to about 10, 15 or 20 mg/mL. In further embodiments, the compositions contain sodium chloride at a concentration of from about 0 mg/mL

R7

R7 cont.

to about 7.5 mg/mL. In another embodiment, the compositions contain sodium chloride at a concentration of 0 mg/mL, 1.5 mg/mL, 6.8 mg/mL or 7.5 mg/mL. In these embodiments, the pharmacologically suitable fluid is aqueous saline.

Please replace the paragraph on page 25, lines 11-21, with the following paragraph:

R8

In certain embodiments herein, the emulsifier(s) is (are) a polyoxyetheylene sorbitan fatty ester or polysorbate, including, but not limited to, polyethylene sorbitan monooleate (Polysorbate 80), polysorbate 20 (polyoxyethylene (20) sorbitan monolaurate), polysorbate 65 (polyoxyethylene (20) sorbitan tristearate), polyoxyethylene (20) sorbitan mono-oleate, polyoxyethylene (20) sorbitan monopalmitate, polyoxyethylene (20) sorbitan monostearate; sorbitan monostearate; sorbitan tristearate; sorbitan monolaurate; sorbitan mono-oleate; or sorbitan monopalmitate. In further embodiments, the emulsifier(s) is (are) polysorbate 80, sorbitan monolaruate or polyoxyethylene (20) sorbitan monolaurate.

Please replace the paragraph on page 27, lines 14-23, with the following paragraph:

R9

The compositions provided herein are prepared by procedures well known to those of skill in the art. For example, a solution formulations may be prepared by the procedure of EXAMPLE 1. Briefly, polyethylene glycol 400 and/or propylene glycol, and a preservative, such as vitamin E TPGS, are mixed at about 42 °C until a homogeneous solution forms. The temperature is lowered and the steroidal anti-inflammatory agent is added. In a second vessel, formoterol fumarate dihydrate and the remaining ingredients are dissolved in approximately 70% water. The two solutions are mixed and the resulting solution is diluted with water to the desired volume.

Please replace the paragraph on page 28, lines 2-4, with the following paragraph:

B10

Standard physiological, pharmacological and biochemical procedures are available for testing the compositions provided herein to identify those that possess bronchodilatory activity.

Please replace the paragraph on page 34, lines 13-23, with the following paragraph:

B11

Polyethylene glycol 400 and/or propylene glycol and vitamin E TPGS were mixed in a stainless steel container with heating at about 42 °C until a homogeneous liquid formed. While maintaining the liquid phase, the temperature was lowered and the steroid active ingredient, *e.g.*, budesonide or fluticasone propionate, was added. The mixing was continued until all of the drug substance had dissolved. In another container all other ingredients, including formoterol fumarate dihydrate, were mixed with about 70% water until a clear solution formed. The two solutions were mixed together until a homogeneous clear solution formed. The volume was made up with water and the solution was mixed to give the desired composition.

IN THE CLAIMS:

Please amend claims 1, 63, 95 and 117 to read as follows:

B12

1. (Amended) A pharmaceutical composition, comprising (i) formoterol, or a derivative thereof; and (ii) a steroidal anti-inflammatory agent, or a derivative thereof;

in a pharmacologically suitable fluid, wherein the composition is stable during long term storage, the fluid comprises water, and the composition is formulated at a concentration for direct administration to a subject in need thereof.

B13

63. (Amended) The pharmaceutical composition of claim 1, wherein the steroidal anti-inflammatory agent is beclomethasone dipropionate, beclomethasone monopropionate, flunisolide, triamcinolone acetonide,